Comparison of Final Infarct Volumes in Patients Who Received Endovascular Therapy or Intravenous Thrombolysis for Acute Intracranial Large-Vessel Occlusions

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IMPORTANCE Studies comparing the efficacy of intra-arterial therapy (IAT) and medical therapy in reducing final infarct volume (FIV) in intracranial large-vessel occlusions (ILVOs) are lacking.

OBJECTIVES To assess whether patients with ILVOs who received IAT have smaller FIVs than patients who received either intravenous tissue plasminogen activator therapy (IVT) or no reperfusion therapy (NRT) and to determine a National Institutes of Health Stroke Scale (NIHSS) threshold score that identifies patients most likely to benefit from IAT.

DESIGN Retrospective cohort study of patients with ILVOs between 2009 and 2011.

SETTING Two large-volume stroke centers.

PARTICIPANTS Adults with anterior circulation ILVOs who presented within 360 minutes from the time last seen as normal. Patients with isolated extracranial occlusions were not included.

EXPOSURE Intra-arterial therapy, IVT, or NRT.

MAIN OUTCOMES AND MEASURES Final infarct volumes, rates of acceptable outcome defined as a modified Rankin Scale score of 0 to 3 at hospital discharge, and NIHSS threshold scores.

RESULTS A total of 203 consecutive patients with ILVOs were evaluated. Baseline characteristics were similar among the 3 groups. The median infarct volume was significantly smaller for the IAT group (42 cm³) than for the IVT group (109 cm³; P = .001) or the NRT group (110 cm³; P < .01). A higher magnitude of infarct volume reduction in more proximal occlusions was noted in the IAT group compared with the IVT and NRT groups combined: internal carotid artery terminus (75 vs 190 cm³; P < .001), M1 middle cerebral artery (39 vs 109 cm³; P = .004), and M2 middle cerebral artery (33 vs 59 cm³; P = .04) occlusions. Patients were stratified based on NIHSS score at presentation (8-13, 14-19, and ≥20). For patients with an NIHSS score of 14 or higher at presentation, IAT significantly reduced FIV (46 cm³ with IAT vs 149 cm³ with IVT or NRT; P < .001) compared with patients with an NIHSS score of 8 to 13 (22 cm³ with IAT vs 44 cm³ with IVT or NRT; P = .40). Patients with an NIHSS score of 14 or higher who received IAT appear to benefit most from IAT.

CONCLUSIONS AND RELEVANCE Our data suggest a greater reduction of FIV with IAT compared with either IVT or NRT. Moreover, patients with an NIHSS score of 14 or higher may be the best candidates for endovascular reperfusion therapy.


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Large-vessel occlusions account for 45% of acute ischemic strokes that occur in patients who present to emergency departments in the United States; many of these patients present outside the time frame for intravenous tissue plasminogen activator (tPA). Intravenous thrombolysis with tPA results in recanalization in less than 5% of internal carotid artery terminus occlusions and in 25% to 30% of proximal middle cerebral artery occlusions. Failure to achieve reperfusion is an independent predictor of poor clinical outcome resulting from large infarcts. Advances in endovascular reperfusion strategies with mechanical devices have enhanced reperfusion rates without concordant improvement in 90-day outcomes. Although it seems that endovascular therapy for intracranial large-vessel occlusion (ILVO) should be more effective in appropriately selected patients, randomized clinical data comparing endovascular therapy with intravenous therapy for large-vessel occlusions are currently lacking. The final infarct volume (FIV) after treatment may be an excellent surrogate for predicting clinical outcome. For a prospective randomized clinical study comparing these 2 treatment modalities, the identification of a population of patients most likely to benefit from endovascular therapy while maximizing applicability of treatment seems to be of prime importance.

To date, no study has demonstrated the benefit of endovascular therapy in reducing infarct volumes in patients with ILVOs. In our retrospective cohort study, we compare FIVs in patients with ILVOs who received endovascular therapy (ie, intra-arterial therapy [IAT]), intravenous tPA therapy (IVT), or no reperfusion therapy (NRT). In addition, we also attempt to define a National Institutes of Health Stroke Scale (NIHSS) threshold score above which IAT is likely to result in a better clinical outcome and lower FIV compared with IVT or NRT.

Methods

Patients
After obtaining appropriate institutional review board approval, we performed a retrospective cohort analysis of all patients with acute ischemic stroke who presented to 1 of 2 academic stroke centers (Grady Memorial Hospital and Emory University Hospital) in Atlanta, Georgia, between 2009 and 2011. The protocols differed between the 2 institutions: patients with an ILVO quickly received IAT at Grady Memorial Hospital, a level 1 trauma center, whereas IAT was uncommonly used at Emory University Hospital, a tertiary referral center, thus allowing for a cohort comparison during the same time period. The neurocritical care protocols used at the 2 centers were similar at the time of our study. A total of 203 consecutive patients met inclusion criteria (ie, >18 years of age, with a time from last seen as normal to first computed tomographic [CT] scan of <360 minutes and with an anterior circulation ILVO). Anterior circulation ILVOs included internal carotid artery (ICA), M1 middle cerebral artery, and M2 middle cerebral artery occlusions. Isolated posterior circulation or anterior cerebral artery occlusions and distal M3/M4 occlusions were excluded. The included cohort was divided into 3 groups: IAT (n = 134), IVT (n = 38), and NRT (n = 31). Patients who received IAT after having received IVT were also included in the IAT group. As a result of the differences in endovascular approaches at the 2 sites, of the 134 patients in the IAT group, 123 (91.8%) were treated at Grady Memorial Hospital; of the 38 patients in the IVT group, 32 (84.2%) were treated at Emory University Hospital; and of the 31 patients in the NRT group, 22 (71.0%) were treated at Emory University Hospital.

Data on baseline characteristics were retrospectively collected from admission and discharge records and included age, sex, vascular risk factors (diabetes mellitus, hypertension, atrial fibrillation, hyperlipidemia, smoking, and congestive heart failure with an ejection fraction of < 30%), time from last seen as normal to initial CT scan, NIHSS score at presentation, Alberta Stroke Programme Early CT Score on initial CT scan, and time to intravenous thrombolysis or time to groin puncture. For the IAT group, data on the rate of successful recanalization, defined as a thrombolysis in cerebral ischemia score of 2B or 3, and on the use of IVT prior to intervention were also collected.

The disposition of the patient with regard to living at home, acute rehabilitation, or living in a nursing facility was recorded. In addition, the modified Rankin Scale (mRS) score was recorded for each patient prior to hospital discharge by the physical therapists and was captured in our retrospective review of the data.

Radiologic Measurements
The level of occlusion was defined based on initial vascular imaging by use of CT angiography, magnetic resonance angiography, or conventional cerebral angiography. For subgroup analysis based on level of occlusion, data on patients with ICA terminus (ICA-T), M1, or M2 occlusions were compared. All included patients underwent imaging either 24 to 48 hours from time of admission by use of magnetic resonance imaging or more than 48 hours from time of admission computed tomography if magnetic resonance imaging was contraindicated. Infarct volume was determined by 2 of the authors (S.R. and R.G.), who measured the area of the infarct on each slice and summed individual slice thicknesses of all outlined areas. The same method was used to measure the FIV on CT scans of the brain more than 48 hours after admission.

End Points
Final infarct volume as measured by use of magnetic resonance imaging or computed tomography was our primary outcome measure. The mean infarct volumes of the 3 groups were compared. Secondary outcome measures included the proportion of patients who achieved an FIV of less than 70 cm³, mortality rates, and final discharge disposition of the patient with regard to living at home. We were unable to compare the 90-day mRS scores because these were not uniformly captured for patients in the NRT and IVT groups.

Statistical Analysis
All analyses were performed using Microsoft Excel, SPSS Version 20.0 (SPSS Inc), and online statistical tools (VassarStats [www.vassarstats.net/]). Median values were compared using the Mann-Whitney test. Categorical variables were analyzed
IAT group had a lower mean FIV than the IVT and NRT groups, a linear regression model was used to determine whether baseline NIHSS score affected clinical outcome or FIV. Provided into tertiles, with an analysis performed to determine analyses. The patients were stratified by NIHSS scores divided for correlation analyses. The Fisher r coefficients. To correlation between 2 groups using the χ2 test. Comparison of the continuous variables among the 3 groups was performed using the Kruskal-Wallis test and between 2 groups using the t test. The Spearman coefficient was calculated for correlation analyses. The Fisher r-to-z transformation was used to compare 2 correlation coefficients. P < .05 was considered statistically significant for all analyses. The patients were stratified by NIHSS scores divided into tertiles, with an analysis performed to determine whether baseline NIHSS score affected clinical outcome or FIV. A linear regression model was used to determine whether the IAT group had a lower mean FIV than the IVT and NRT groups, controlling for age and NIHSS score, with infarct volume as the dependent variable.

Results

The mean (SD) age of the 203 patients analyzed was 65.9 (15.7) years, and their median NIHSS score was 19 (IQR, 14-23) (Table). The majority of patients (91 [67.9%]) in the IAT group received full-dose intravenous tPA prior to endovascular therapy. The devices used in the IAT group were as follows: penumbra (84 patients [62.7%]), Mechanical Embolus Removal in Cerebral Ischemia (56 patients [41.8%]), and stent-retriever devices (18 patients [13.4%]). Of the 134 patients in the IAT group, 43 (32.0%) used the required use of more than 1 device, and 16 (11.9%) received only intra-arterial tPA. Our Table summarizes the baseline characteristics of the patients in the 3 groups. There were no differences except for the IVT group having a shorter interval from last seen as normal to initial CT scan compared with the NRT group.

The median FIV was significantly smaller in the IAT group (42 cm³ [IQR, 22-108 cm³]) than in the IVT group (109 cm³ [IQR, 39-235 cm³]) and the NRT group (110 cm³ [IQR, 60-190 cm³]) (P = .001) (Figure 1A). There was no significant difference in median FIV between the IAT and NRT groups. The median FIV did not differ between patients who did receive intravenous tPA prior to IAT and those who did not (P = .90). In multivariate linear regression modeling controlling for age, baseline NIHSS score, and interval from last seen as normal to initial CT scan, the median FIV in the IAT group remained significantly lower than it did in the NRT and IVT groups (P < .001), with a Durbin-Watson statistic of 1.96.

For further analyses, we pooled the IVT and NRT groups together for subgroup analyses (ie, the IVT/NRT group) based on location of ILVO. Infarct volumes (Figure 1B) in patients with ICA-T occlusions who received IAT were significantly smaller (median volume, 75 cm³ [IQR, 38-150 cm³]) than those in patients in the IVT/NRT group (median volume, 190 cm³ [IQR, 140-287 cm³]; P < .001). Infarct volumes in patients with M1 occlusions who received IAT (median volume, 39 cm³ [IQR, 20-90 cm³]) were also significantly smaller than those in patients in the IVT/NRT group (median volume, 109 cm³ [IQR, 40-221 cm³]; P = .002). For M2 occlusions, patients in the IAT group had smaller infarct volumes (median volume, 33 cm³ [IQR, 14-48 cm³]) than did patients in the IVT/NRT group (median volume, 59 cm³ [IQR, 32-100 cm³]; P = .04).

In this cohort, IAT resulted in a greater chance of achieving an infarct volume of 70 cm³ or less compared with IVT or NRT in all patients with ILVOs (65.7% [88 of 134] vs 42.0% [29 of 69]; P = .001), ICA-T occlusions (47.2% [17 of 36] vs 7.1% [1 of 14]; P < .01), and M1 occlusions (62.0% [49 of 79] vs 40.5% [17 of 42]; P = .03). The baseline NIHSS score was associated with FIV in both the IAT (R = 0.23, P = .01) and IVT/NRT groups (R = 0.49, P < .001). However, in the IAT group, this correlation was much weaker than it was in the IVT/NRT group (R = .04). The Alberta Stroke Programme Early CT Score at presentation was also inversely correlated with FIV in the IAT (R = −0.46, P < .001) and IVT/NRT groups (R = −0.51, P < .001), although there was no significant difference in the strength of correlation between the 2 groups (P = .70) regardless of the significant differences in FIV between the 2 groups.

We then sought to determine a threshold for IAT based on initial NIHSS score, at which differences in FIV are observed. Patients were stratified based on NIHSS score at presentation (ie, 8-13, 14-19, and ≥20). Infarct volumes in each of these sub-
groups were compared between the IAT and IVT/NRT groups. For patients with an NIHSS score of 14 to 19 or of 20 or more, infarct volumes were significantly smaller in patients who received IAT (Figure 2A). No differences were observed for patients with an NIHSS score of 8 to 13. To determine the threshold for endovascular therapy to achieve a favorable clinical outcome, we used an mRS score of 3 or less at hospital discharge as a marker for “acceptable” outcome and an mRS score of 2 or less at hospital discharge as a marker for “good” clinical outcome. The proportion of patients with an NIHSS score of 8 to 13 who achieved an mRS score of 3 or less at hospital discharge and the proportion of patients with an NIHSS score of 8 to 13 who achieved an mRS score of 2 or less at hospital discharge were similar in the IAT and IVT/NRT groups. An mRS score of 3 or less at hospital discharge was more frequent in patients with an NIHSS score of 14 or greater at presentation, endovascular therapy significantly reduced infarct volume (46 vs 149 cm³; \( P < .001 \)), and these patients had a higher likelihood of achieving a good outcome (20.2% [23 of 114] vs 8.2% [4 of 49]; \( P = .04 \)) or an acceptable outcome (35.1% [40 of 114] vs 10.2% [5 of 49]; \( P = .002 \)) at hospital discharge. For patients who had an ILVO and an NIHSS score of 14 or less at presentation, there was no differ-
ence between endovascular and intravenous or conservative therapies for improving radiologic or clinical outcomes.

Discussion

Our study demonstrates 2 important findings. The first is that patients presenting with an ILVO who received IAT have smaller FIVs than do patients presenting with an ILVO who received either IVT or NRT, which is reflective of reperfusion. This beneficial effect of IAT is greatest in patients with more proximal occlusions. Second, there may be a pretreatment NIHSS threshold score that should be considered when selecting patients for IAT. Our results suggest that this threshold score may be 14 or greater and may be reflective of patients with larger areas of tissue at risk. This threshold was predictive of improved radiologic and clinical outcomes in our patient population.

The adoption of IAT as part of the armamentarium to treat ILVO in ischemic stroke is evolving with rapid technological advances that have aided in achieving high rates of recanalization. Despite mounting evidence that shows the association between recanalization and better clinical outcomes, to date, there has been no randomized controlled trial showing the benefits of mechanical IAT over medical therapy. The design of such a trial will require optimizing the patient population most likely to benefit from IAT, and the present study points to a potential NIHSS threshold score and clot location most likely to benefit from IAT, and the present study points to a potential NIHSS threshold score and clot location that should be considered in such a trial.

Several endovascular device trials have been performed to assess the safety and efficacy of recanalizing an occluded vessel. The selection criterion for such studies has included patients with an NIHSS score of 8 or greater, with the focus on showing the success of revascularization. When comparing the first-generation thrombectomy devices with the more recent stent retrievers, we found that there has been a substantial increase in the rates of successful recanalization. Yet, the clinical outcomes have not been concordant with the increases in recanalization. The trials were performed to obtain 510(k) process clearance of their devices and to prove that authors were able to achieve recanalization in the target vessel. Such data cannot be used to properly power future randomized trials owing to the lack of uniformity across trials and the lack of a consistently used clinical primary endpoint.

There is mounting evidence for the ineffectiveness of intravenous tPA to lyse a thrombus in more proximal vessels. Patients with ICA-T occlusions who received IVT have rates of recanalization as low as 4.4%. The length of the clot may also be useful in determining the likelihood of success with intravenous thrombolysis. Clots more than 8 mm in length have a low probability of recanalization after intravenous thrombolysis. These studies show the potential limitations of IVT for an ILVO. Our study assesses the effect of proximal arterial occlusion on FIV in patients who received IAT, IVT, or NRT. The magnitude of effect of IAT on FIV compared with IVT/NRT is more substantial for ICA-T occlusions than for M2 middle cerebral artery occlusions. Excluding M2 middle cerebral artery occlusions from clinical trials with IAT should be considered because the potential benefit of IAT in this population may be of a lower magnitude compared with more proximal occlusions. The level of occlusion and the baseline NIHSS score are crucial for determining the optimal patient population that can benefit from IAT.

We have found that patients with an NIHSS score of 14 or greater may have the highest probability of benefiting from IAT. The recently published Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke trial showed that 40 of 106 patients (37.7%) in the treatment arm with a baseline NIHSS score of 8 to 14 achieved a good clinical outcome, whereas only 8 of 63 patients (12.7%) with a baseline NIHSS score of greater than 14 achieved a good clinical outcome. For patients with an NIHSS score of 20 or greater in the European Cooperative Acute Stroke Study III, 16% in the IVT arm achieved good outcomes compared with 8% in the placebo arm. Although there was no stratification around the threshold score of greater than 14, for patients with an NIHSS score of 10 to 19, 34% in the IVT arm and 31% in the placebo arm achieved good outcomes. Given the evidence from our analysis and the evidence from recent prospective randomized trials showing that patients with a higher NIHSS score tend to have low rates of good clinical outcomes, a higher NIHSS threshold score as an entry criterion may be warranted when designing future randomized controlled trials with IAT.

A strength of our study is that our cohort was derived from 2 large-volume stroke centers in the same city with different approaches to the treatment of patients with an ILVO. Of the 134 patients in the IAT group, 123 (91.8%) were treated at Grady Memorial Hospital. Of the 69 patients in the IVT and NRT groups, 52 (75.3%) were treated at Emory University Hospital. Other single-center studies addressing a similar question are limited by the bias toward an aggressive or restrictive endovascular approach to stroke therapy at the individual center. The baseline characteristics of the patients were also comparable between the 2 sites.

A limitation of our analysis is the lack of 90-day clinical outcomes in the NRT and IVT groups. Instead, we used the mRS score at hospital discharge as a measure of clinical outcome. The immediate goal of any reperfusion strategy is to limit FIV by timely revascularization. Because the FIV is strongly correlated with 90-day outcomes, we believe that this is a reasonable surrogate of clinical outcome. Another limitation of our study is the lack of a uniform algorithm for patient selection for IAT and for the selection of the reperfusion devices used. Thus, the results that we report may vary from those of other centers. Nonetheless, the overall outcome rates and reperfusion rates are in the range of the published literature. We did not assess all patients who received IVT in this analysis, and we only considered those patients with a persistent large-vessel occlusion. The aim of this analysis was to assess the patients who received IVT but whose arteries did not recanalize because they would be theoretical candidates for clinical trials assessing the utility of IAT after the failure of IVT. Differences, if any, in the neurocritical care protocols between the 2 centers were not accounted for. Lastly, our study is retrospective and thus reflects the inherent biases of such an analysis. The exploratory analysis provides a framework and guid-
ance for prospective trials and may provide some insight for trials currently being implemented to test the efficacy of IAT compared with IVT.

In conclusion, our results suggest that the patients most likely to benefit from IAT are those with a more proximal ILVO who have an NIHSS score of 14 or greater at presentation. Our findings can help others to identify the patients most likely to benefit from IAT and can provide a basis for designing future clinical trials to assess the efficacy of IAT compared with medical therapy.

REFERENCES